DEVELOPMENTAL POSTERIOR ENTERIC REMNANTS AND SPINAL MALFORMATIONS*

THE SPLIT NOTOCHORD SYNDROME

BY

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Clinicians have only recently recognized the aetiological factors that connect a wide variety of developmental anomalies of the skin of the back, the spine, the central nervous system and the gut (Beardmore and Wiglesworth, 1958; Nathan, 1959). Starting with the observations of Lereboullet (1863) on the formation of sagittally split embryos from artificially inseminated pike ova, evidence has slowly accumulated which shows their common origin from a single aberration of development.

The many publications in the intervening years dealing with these apparently dissociated malformations have been difficult to correlate, due to variations in both terminology and suggested aetiology. The purpose of this paper is: (i) To summarize the embryological background to the concept of the split notochord syndrome; (ii) to suggest a generic title for the group of anomalies and a nomenclature for the gut components ; (iii) to describe five illustrative cases; and (iv) to give key references to the relevant literature.

The split notochord syndrome embodies lesions that have been described under the following titles:

> Anterior and combined spina bifida; 'butterfly vertebra'; diastematomyelia; diplomyelia; Klippel-Feil syndrome; accessory or persistent neurenteric canal; dorsal intestinal fistula; spinal and cranial cysts; post-vertebral 'teratomatous' or dermoid cysts and sinuses; pre-vertebral, mediastinal or mesenteric cysts; some enteric 'duplications' or diverticula; vesico-intestinal fissure and certain intestinal malrotations and diaphragmatic herniae.

Embryology

An embryo may develop with partial duplication and separation of the notochord, the level and extent of the separation being variable; this results in a gap developing in the dorsal tissue mass between the two parts of the notochord (Figs. 1 and 2). Through this gap the ventrally situated yolk sac or gut anlage endoderm will herniate and it eventually adheres to the dorsal ectoderm or skin anlage (Figs. 3 and 4). The hernia may rupture to produce a fistula from the yolk sac into the amniotic cavity which separates the halves of the future cord and spine (Fig. 5). Subsequent differential growth of the embryo tends to close and obliterate the fistula and the extent of residual lesions depends on the success attained by this process. Thus the development of the base of the skull, vertebral column and central nervous system may be affected as well as gut, while sequestration of dorsal ectoderm may lead to dorsal dermoid cysts and sinuses. Persisting remnants of yolk sac origin may differentiate into tissues characteristic of any part of the gut or its embryological derivatives such as lung, etc. (Figs. 6, 7, 8, 9). Differential growth of gut and vertebral column leads to wide separation of the areas affected in each, as in long diverticula originating within the abdomen and passing through abnormal openings in the diaphragm to a high thoracic vertebral attachment. Furthermore, abnormal fixation of gut to the vertebral column may cause subsequent failure of rotation.

Clinical Presentation

Hitherto all the consequent malformations have been considered individually as extreme rarities, but if they are grouped the basic pattern is found to be fairly common.

These malformations may be considered to fall into two broad classes: (*a*) visceral malformations, and (*b*) spinal and central nervous malformations.
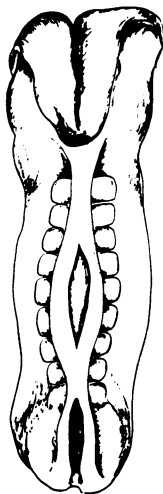
FIG. 1.—Anomalous embryo (2 mm.) with split notochord ('ring embryo').
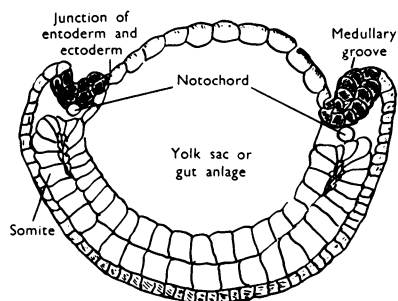
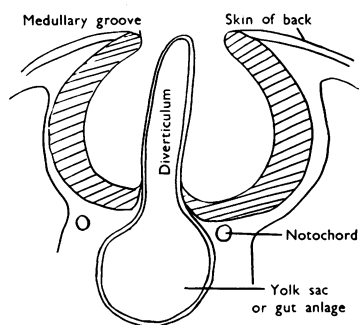FIG. 2.—Section across anomalous embryo with split notochord.

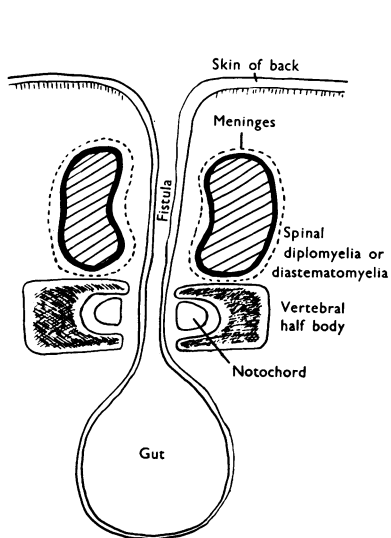FIG. 3.—Posterior diverticulum of yolk sac developing between split elements of notochord.

FIG. 4.—Early stage in evolution of developmental posterior enteric fistula.
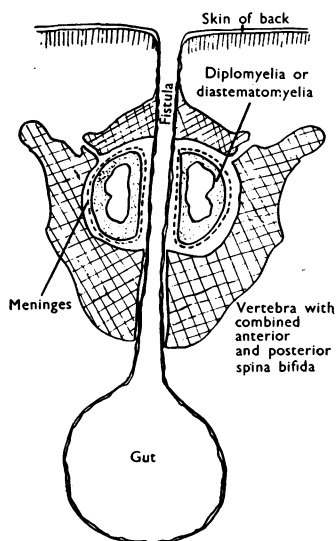
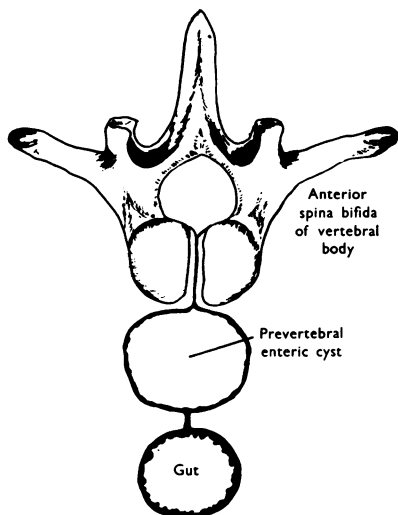FIG. 5.—Established developmental posterior enteric fistula.

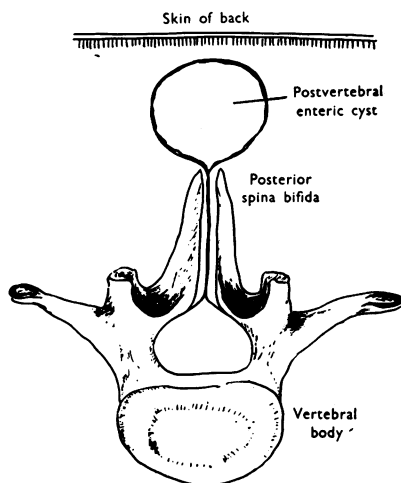FIG. 6.—Prevertebral developmental posterior enteric cyst.

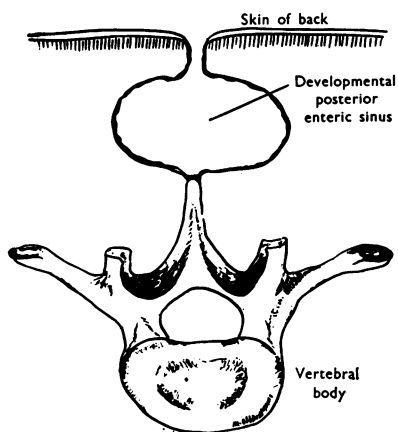FIG. 7.—Postvertebral developmental posterior enteric cyst.
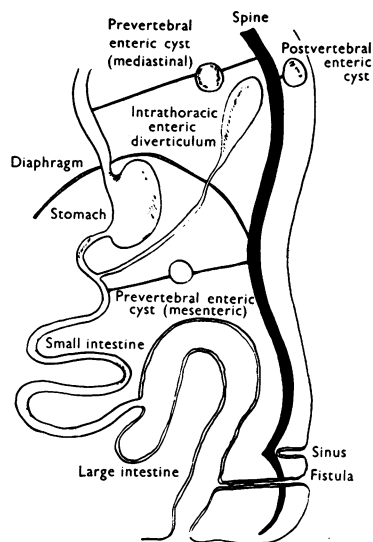

FIG. 8.—Developmental posterior enteric sinus.

FIG. 9.—Distribution of developmental posterior enteric remnants.

(*a*) **Visceral Malformations.** The theoretical considerations accord well with the observed developmental anomalies classed in this paper as posterior enteric remnants. These may comprise certain mesenteric or posterior mediastinal 'duplications', diverticula or cysts connected by fibrous strands to the anterior aspect of the body of a vertebra situated cephalad to the enteric remnant. The vertebral body concerned is often bifid, and a complete anterior and posterior spina bifida occasionally exists.

Histological examination of the remnant will usually show the presence of smooth muscle and enteric mucosa in the walls of the lesion. The mucosal type may differ from that of the gut to which it lies adjacent, and it may be flattened and atrophic, the appearance giving no clue to its derivation. Occasionally broncho-pulmonary or other tissues primarily derived from the developing gut will be present.

The developmental posterior enteric remnants may be subdivided as follows:

(1) FISTULAE. When obliteration of the embryonic fistula fails completely the track passes back from the gut through the mesentery or mediastinum, traverses a complete spina bifida which may be coupled with a diastematomyelia or diplomyelia, to open on the skin in the midline of the back.

(2) SINUSES. The dorsal part of the embryonic fistula is all that persists. It forms a sinus derived from cutaneous or enteric tissues that passes forward from the midline of the skin of the back. There may be an underlying posterior or complete spina bifida.

(3) POSTERIOR ENTERIC DIVERTICULA. The ventral part of the embryonic fistula remains and communicates with the gut. There may be an associated anterior spina bifida or fibrous adhesion to a vertebral body.

(4) POSTERIOR ENTERIC CYSTS. Only an intermediate part of the embryonic fistula or diverticulum persists and the atrophic portions are represented by fibrous bands. These cysts may be prevertebral (posterior mediastinal or mesenteric), vertebral (spinal or mid-brain) or postvertebral in position. Many examples of the latter have been classed as teratomatous cysts. Anterior, combined or posterior spina bifida can be associated lesions.

Bremer (1952) proposed the term 'dorsal intestinal fistula' to cover this group of anomalies, a term we reject as so few of the lesions are true fistulae. The term 'enteric duplication' has also been applied to some of these lesions, causing confusion, as it should be restricted to anomalies attributable to defects of

embryonic vacuolation of the gut, an entirely different process (Bremer, 1944).

Malformations of the heart and great vessels, oesophageal atresia and hiatus hernia have also been observed in association with defective spinal development. Whilst their coincidence is compatible with the theory of the split notochord, positive evidence is lacking.

(*b*) **Spinal and Central Nervous Malformations.** The gap in the dorsal tissue mass of the embryo, which is associated with a split notochord, may close without trace in the process of development. When this closure is less than complete the resultant spinal defect may range from a slight widening of the vertebrae to a complete anterior and posterior spina bifida. Minor degrees of anterior spina bifida produce the radiological appearance known as 'butterfly vertebrae', which may not be demonstrable without tomography. The more gross lesions may enclose enteric or cutaneous elements, as has been indicated. Pairs of hemivertebrae in these lesions may assume individual (if distorted) growth; fusion of the medial pedicles so formed results in the bony spur found with diastematomyelia (Fig. 10)
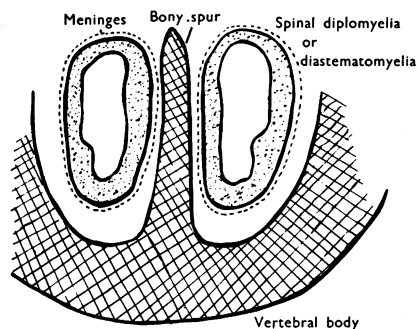

FIG. 10.—Diastematomyelia.

(Bremer, 1957). In this connexion it is noted that fusion of the cervical vertebrae constitutes the osseous element in the Klippel-Feil syndrome, and that these vertebral bodies are often split.

The spinal canal is widened in each of these types of vertebral modification, and anterior or posterior meningocoeles may protrude where the spine is bifid. When the spinal cord itself is cleft, the separated halves seldom rejoin inferiorly, possibly due to tethering by the nerve roots. Each half of the cord is invested in meninges derived from the spreading mesenchyme, and the two median walls of the dura and arachnoid may fuse to form a sheet of tissue

which contains any remnant of an enteric fistula. Within the meninges each half of the neural groove develops, either as the lateral half of a spinal cord (diastematomyelia) or as one of a pair of whole but malformed cords (diplomyelia) (Herren and Edwards 1940). During late foetal life the spinal cord migrates up the spinal canal and the injured segment becomes separated from the bony lesion, a process which can be limited by the anchor of a long bony spur. Matson, Woods, Campbell and Ingraham (1950) describe the clinical picture and the relief of symptoms consequent on excision of the spur.

The visceral, cutaneous, spinal and nervous lesions described so far in relative isolation may coincide in a variety of combinations, while hamarto-matous malformation of the affected tissues not infrequently contributes to their bizarre nature.

Clinical Reports

Various manifestations of the split notochord syndrome within the chest and abdomen have frequently been described in detail under a variety of titles. There are fewer records of posterior enteric remnants situated within or behind the vertebral column, and five of these cases are there-fore described. Three are personal cases, and the others were recognized in the library of recent clinical photographs. The number in no way reflects the total experience of the condition at the Royal Hospital for Sick Children, Glasgow.

Case 1. M.F. This girl was seen by Mr. Matthew White at the age of 11 years when she began to get attacks of pain in the left thigh precipitated by coughing. She had a limp and the left lower limb was ½ in. shorter than the right. A sinus 1 in. in diameter opened over the lumbo-sacral spine (Fig. 11); the surrounding tissues were tender but there was no neural deficit. Radiographs revealed a complete spina bifida of the lumbar spine and upper sacrum. A sinogram outlined the sinus to the laminae, and this part of the track was excised. The pathologist described it as a dermoid growth composed of skin elements and embryonic lung tissue. The lining was partly squamous epithelium in which were sebaceous glands and hair follicles. Adjacent were differentiated cartilage, embryonic bronchial cartilage and primitive lung tissues. The ciliated epithelium lining the bron-chioles was supported by actively secreting mucous glands.

The sinus persisted but the girl remained well for four years, then being admitted to the Orthopaedic Unit, Western Infirmary (Mr. R. Barnes) with severe left sciatica of two weeks' duration. She was toxic and febrile to 102° F. with a fluctuant swelling above the sinus. She responded to treatment with sulphadiazine; penicillin and achromycin were ineffective.

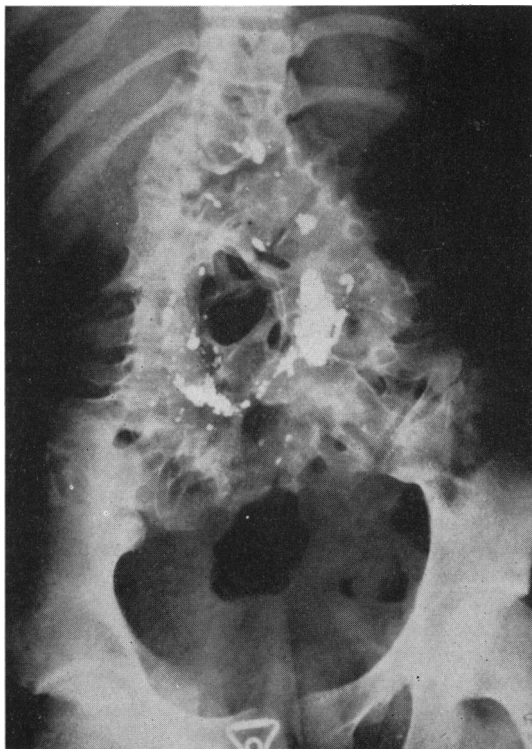FIG. 11.—Case 1. Developmental posterior enteric sinus.

FIG. 12.—Case 1. Cysternal myelogram consistent with diastemato-myelia.

Subsequent investigations included a cysternal myelogram. The contrast medium ran down to the lumbar lesion and outlined both sides of a solid swelling 'within the canal' (Fig. 12). Stereoscopic studies revealed a flake of bone consistent with diastematomyelia in the upper lumbar spine. The cerebrospinal fluid was normal (Lange negative, protein 30 mg. %, sugar 50 mg. %, chlorides 714 mg. %).

After three and a half months' bed rest the child was discharged symptom free, only to be readmitted 10 months later for a further two months because of recurrent left sciatica. She was again pyrexial and toxic with a diffuse, tender, non-fluctant swelling of the left thigh and buttock extending to the lumbo-sacral area. The leucocyte count was 25,000 c.mm., the urine was normal and a blood culture proved sterile. The left femoral radiograph was normal. Urgent exploration of the left thigh opened an abscess deep to the tensor fasciae latae, yielding two and a half pints of pus from which coliform organisms were cultured.

She received tetracycline and responded well, but sinuses intermittently discharged from the left thigh and lumbo-sacral skin. This persisted for 10 months after she left hospital and she was therefore readmitted. Secondary infection with penicillin-sensitive *Staphylococcus aureus* had now occurred, the sinuses following the course of the previous abscess cavity. Healing was not promoted by systemic penicillin, so local instillation of chloramphenicol was tried. After treatment for one month an abscess reformed from the spinal defect and again *Escherichia coli* was isolated from the pus. Further drainage and chloramphenicol instillations sterilized the cavity, leaving a chronic sinus. After eight months in hospital, treatment was continued in the out-patient department and healing has slowly occurred.

Case 2. O.C. This girl was admitted under the care of Mr. Andrew Laird four days after premature birth with a gross malformation of the back. Bowel herniated extensively through the centre of the lumbo-sacral region forming a 'prolapsed natural colostomy' with exposed intestinal mucosa. The stoma was at the lower part of the prolapse and through it a catheter was passed into a prolapsed rectum (Fig. 13). Radiographs of the spine show duplication below the second lumbar vertebra and prolapse of gut backwards through the spinal defect (Figs. 14 and 15). Active treatment was not attempted and the infant died at home after eight days in hospital.

Case 3. F.McL. This boy was admitted to Mr. Dennison's wards at the age of 4 weeks. A hemispherical swelling 1 in. in diameter protruded in the midline over the upper sacrum. The basal two-thirds of the swelling were covered by normal skin and the apical third with mucous membrane which showed intermittent waves of peristalsis. In the centre mucus exuded from the orifice of a sinus (Fig. 16). This 7 lb. 6 oz. infant appeared normal in all other respects, including radiographs of the spine and barium studies of the gut, apart from a skin dimple below the lesion.

The lesion was excised together with the skin dimple, to which a narrow fibrous pedicle arose from the sacral hiatus. Healing was uncomplicated.

The excised ellipse of skin measured $3 \times 2 \cdot 5$ cm. and its centre looked like an enterostomy stoma from which a sinus penetrated just short of the deep surface of the specimen. Microscopy showed the skin to become continuous with a blind pouch of small intestine complete in all its layers. There was no evidence of meningocoele (Fig. 17).
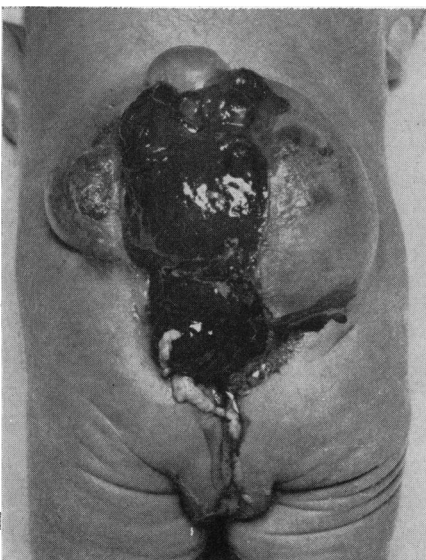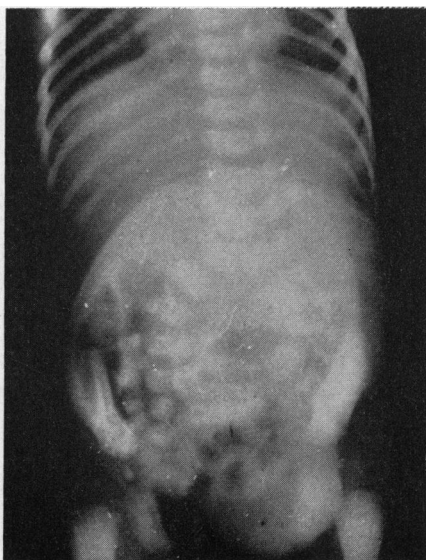

FIG. 13   FIG. 14   FIG. 15

FIGS. 13 to 15.—Case 2. Developmental posterior enteric fistula. Radiographs of spine. Complete spina bifida.
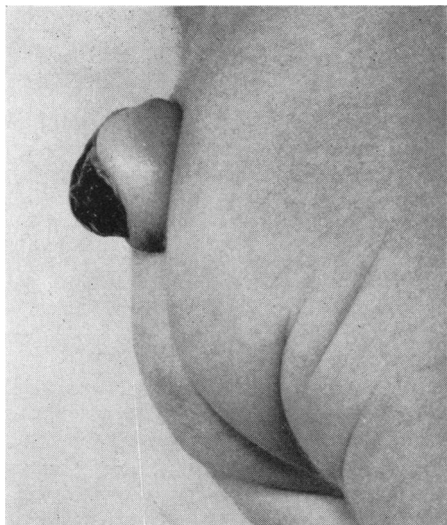
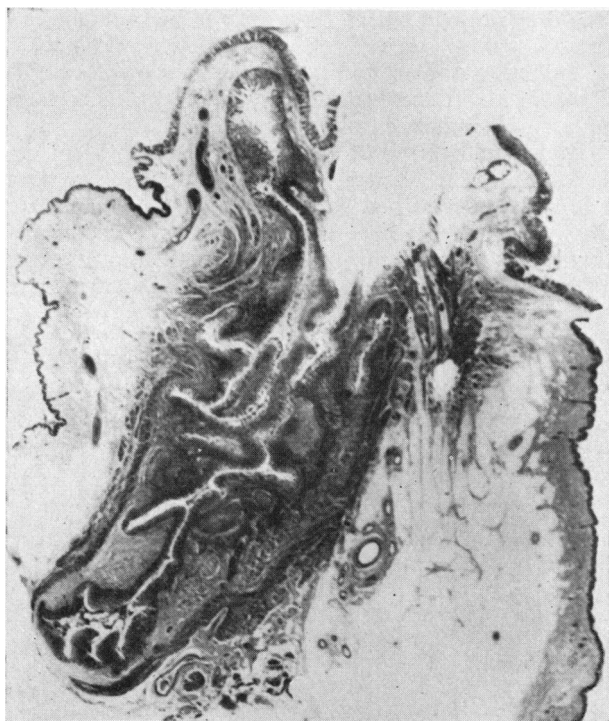FIG. 16.—Case 3. Developmental posterior enteric sinus.

FIG. 17.—Case 3. Microscopic appearance of excised sinus.

Case 4. A.G. This 6 lb. 1 oz, girl was admitted to Mr. Dennison's wards within 24 hours of her birth at term. Her general health was good, but a meningocoele 3·5 cm. in diameter covered by thin intact skin arose from the lower thoracic spine. Beneath the sac was an umbilicated red area 1 cm. in diameter, which had a smooth moist surface changing abruptly to normal skin at the periphery. The umbilication twitched slightly coincident with inspiration, and a probe was passed to 7 mm. An ill-defined soft swelling 2·5 cm. in diameter, covered by normal skin and with a bony spur palpable in its depths, extended on each side of the red area from below (Fig. 18a). A lower dorsal combined spina bifida was shown radiographically (Fig. 18b).

On the third day the meningocoele was excised with ligation of a narrow pedicle. The umbilicated lesion was found to be flanked by loose fatty tissue resembling infantile omentum but containing some muscle. The inspiratory retraction of the red dimple ceased when it was isolated to its pedicle, which emerged from an orifice, incomplete above, in the apex of a cone of fused spinous processes. The lesion was excised without removal of bone or exposure of the spinal cord. The child was discharged well and healed on the twenty-fifth post-operative day.

Microscopy confirmed the absence of nerve tissue in the meningocoele. The umbilicated area was covered by poor squamous epithelium, ulcerated in places. The track penetrating the deeper tissues was lined partly by squamous and partly by respiratory epithelium, and mucous glands were present in the wall. No smooth muscle was seen, but striated muscle and cartilage were in close proximity. The skin around the lesion showed an excess of the normal appendages in the dermis (Fig. 19).

Case 5. M.G. This 8½ lb. boy was admitted 24 hours after a normal birth at term. In addition to exstrophy of the bladder he had intestinal obstruction due to anal agenesis. His rudimentary scrotum was bifid and the testes were undescended. The two halves of the pelvis were separated not only anteriorly but also posteriorly where the sacrum was bifid. Projecting backwards from the apex of the sacral cleft was a bony spur entering a globular mass of tissue covered by skin bearing small flat haemangiomatous areas. A bulging smooth red membrane occupied the lower part of the cleft, and a small meningocoele arose from above the bony spur. Limited active movement was seen in the lower limbs (Fig. 20).

Treatment was limited to excision of the meningocoele with the bony spur and tissue mass, and left iliac colostomy under local anaesthesia. Chromosomal sexing was established from buccal smears. Although the child appeared to thrive he died suddenly and unexpectedly on the tenth day.

No specific cause of death was apparent at autopsy, which demonstrated the additional presence of a mild hydrocephalus without Arnold-Chiari malformation. The rectum was found to be a blind pouch passing back between the ureters to form the bulging membrane that occupied the lower part of the sacral cleft, and this membrane was covered on both its surfaces with intestinal mucosa (Fig. 21). The tissue mass excised at operation proved to be a teratomatous dermoid containing a developing tooth.

FIG. 18a.—Case 4. Developmental posterior enteric sinus.
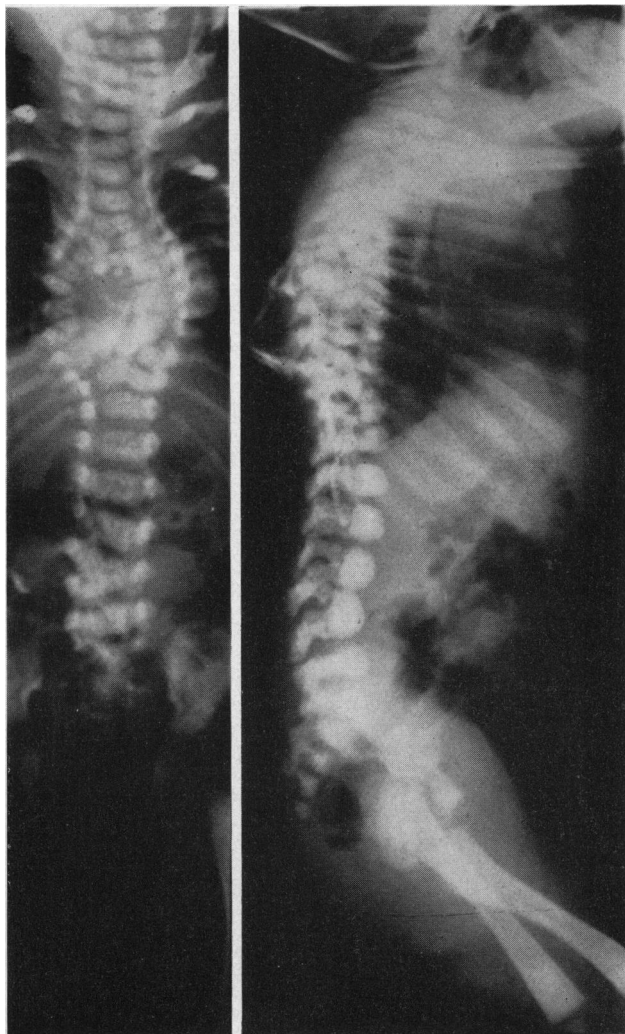

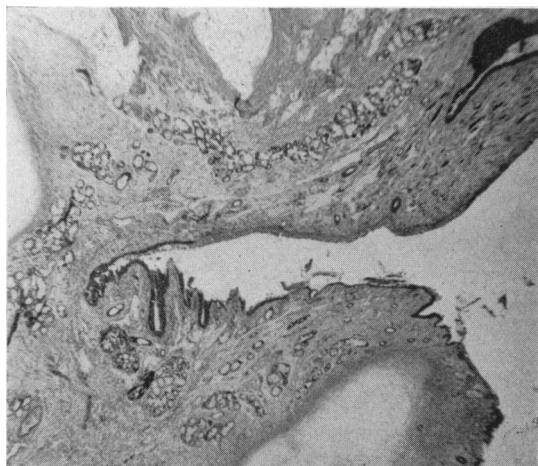FIG. 18b.—Case 4. Radiographs of spine.

FIG. 19.—Case 4. Microscopic appearance of excised sinus.

FIG. 20.—Case 5. Developmental posterior enteric sinus with meningocoele, dorsal teratomatous dermoid and exstrophy of bladder (vesico-intestinal fissure).
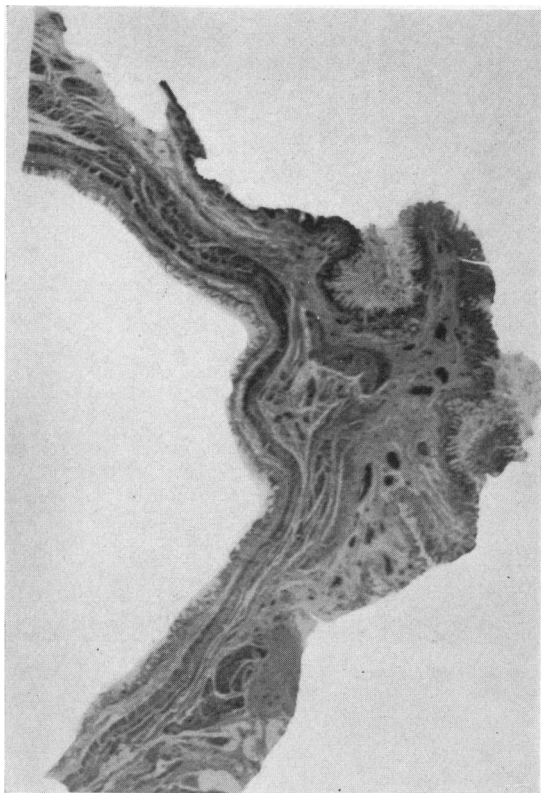

FIG. 21.—Case 5. Microscopic appearance of membrane lying in sacral cleft.

Case Commentary

The first patient is exceptional in having reached the age of 18 years in relatively good general health. In addition to her combined anterior and posterior spina bifida, diastematomyelia with a bony spur and splitting of the meninges investing the spinal cord have been demonstrated. The pulmonary tissues in the excised sinus have shown potentialities comparable with the foetal fore gut, whilst the repeated coliform infections which followed the partial excision raise the possibility of a tiny fistulous connexion with the gut. The second patient is an uncommonly gross example of a fistula from the hind gut. Peristaltic activity in the third case is remarkable, the enteric sinus lacking any residual connexion with the gut. The fourth case may be contrasted; here muscle contraction coincided with inspiration, suggesting that an abnormal branch from a phrenic nerve activated the striated muscle in a remnant which remotely caricatured bronchial elements. The fifth patient has a form of vesico-intestinal fissure (Hall, McCandless and Rickham, 1953) showing a dorsal teratomatous dermoid in association with posterior enteric diverticulum. The existence of intestinal mucosa on both surfaces of the terminal membrane of the diverticulum is consistent with it having been formed by the process of pinching off an embryonic fistula. The defects in the perineum and lower abdominal wall are consistent with a linear midline cleft of the caudal end of the embryo and modern concepts of the aetiology of exstrophy of the bladder (Glenister, 1958).

Discussion

The researches of Lereboullet (1863) on the effects of artificial insemination on the ova of the pike showed some of the resultant embryos to be split sagittally between a normal head and tail, the yolk sac being exposed centrally in the dorsal gap. By destruction of the first daughter cell of the frog ovum Roux (1888) produced embryos which were split but incomplete, but it was Hertwig (1892) who showed the production of true 'ring embryos' in the frog by fertilization of post-mature ova; he accepted the dorsal clefts as a variation of the neurenteric canal or blastopore, appreciated their role in the production of combined spina bifida, and coined the word diastematomyelia. Similar changes have been produced in mammalian embryos (Warkanay, 1960),

Oehlecker (1909) emphasized that the commoner variety of posterior spina bifida is the result of a separate and distinct anomaly occurring much later in foetal life, but where there has been a complete spina bifida anterior fusion and repair leaves a

persisting posterior defect. With both varieties of spina bifida there may be hamartomatous changes in the overlying tissues, often classified as teratomata (Nicholson, 1937).

Svitzer (1839) claims the first clinical description of combined spina bifida, the anterior cleft of which was traversed by coils of gut, and Muscatello (1894) reviewed a number of comparable cases. Lucksch (1903) described a still-born infant with an intestinal fistula traversing an upper dorsal spinal defect, and Keen and Coplin (1906) reported a patient with a congenital rectal fistula of bronchial structure that passed through the sacrum and cauda equina to open on the skin of the back. The Committee on Spina Bifida, Clinical Society of London, in their Report (1885), recognized that duplication of the centre of vertebral bodies could be associated with bony spurs dividing the spinal cord.

The modern concepts which link the observations on animal embryos with the clinical findings in man have been developed mainly by Saunders (1943), who more recently extended his theory jointly with McLetchie, Purves and Saunders (1954). Very similar conclusions were reached independently by Bremer (1952) and the introductory outline of this paper is based on the work of these authors.

Hertwig's theory that complete vertebral clefts are due to arrest of the normal fusion of the blastopore lips laid the foundations of discussion. The views of Budde (1912, 1926), Adelmann (1920), Gruber (1923, 1926) and Bell (1923) included speculation on the applicability of this theory to mammals. Gruber (1926) estimated the time of development of the anomaly and the role of mechanical compression, and Budde (1926) suggested that persistence of the primitive streak could provide an abnormal ento-ectodermal connexion.

Discounting Hertwig's theory, Feller and Sternberg (1929) suggested that a cell rest from the primitive knot (Hensen's node) persists and causes a cleft notochord; Korff (1937) further postulated proliferation of the cell rest to form an abnormal organ. These workers were the first to draw attention to the importance of the cleft notochord, an anomaly seen in human embryos by Johnston (1931) and Frazer (1931). The migration of the primitive knot with growth discounts the possibility of its derivatives splitting the notochord. The knot lies in the blastopore lip of the normal neurenteric canal, a minute tube which exists for a brief period connecting yolk sac and amniotic cavity; subsequent embryonic growth and development are such that the remains lie finally at the tip of the coccyx, caudal to any spinal lesion. For this reason Bremer (loc. cit.) avers that the lesion in the 'ring embryo' is an 'accessory neurenteric canal' and a perversion rather than an arrest of normal development.

An alternative theory proposed by Fallon, Gordon and Lendrum (1954) postulates an upset in the normal process of excalation of the notochord, which occurs in the third week of foetal life (Keith, 1948). They were influenced by the work of Stoeckel (1935) and Veeneklaas (1952), who noted the intimate contact of the endoderm with the notochord in early foetal life, and by the description by Patten (1946) of a 6-mm. human embryo with local kinking and fusion of the notochord to the neural tube. One of the authors has since abandoned this conception of the embryology in favour of that of Saunders (Lendrum, 1958).

Saunders (loc. cit.) has emphasized that anterior or combined spina bifida most frequently involves the cervical and cervico-dorsal vertebrae and many affected infants are still-born with skull defects or anencephaly; stomodeal duplication occurs occasionally (Morton, 1957). As the cephalic end of the notochord develops first this is in accordance with the theory of Stockard (1921) that an organ is most sensitive to disturbances in development at its moment of inception.

Summary

Evidence is presented that an abnormal splitting of the notochord, known to occur in the developing embryo, can cause a wide variety of malformations. These may involve the viscera of the chest or abdomen and incorporate abnormal tissue remnants of enteric derivation; they include combined spina bifida and allied vertebral malformations, together with associated central nervous anomalies and defects in the development of the skin and subcutaneous tissues of the back.

Hitherto these malformations have been individually named; it is now suggested that they can be usefully classified together as manifestations of the 'split notochord syndrome'. Their apparent rarity has been due to failure to appreciate the common basic aetiology.

A terminology is suggested for the abnormal structures of enteric origin in this group. They are classed as developmental posterior enteric remnants, be they fistulae, sinuses, diverticula or cysts.

Five illustrative cases displaying these enteric remnants are described.

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